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Development of an Alkyne-de Mayo Reaction for the Synthesis of Medium-Sized Carbacycles and Cyclohepta[*b*]indoles

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Dedicated to Prof. H.-J. Knölker on occasion of his 60th birthday.

Abstract: *Embedded medium-sized carbacycles and cyclohepta[b]indoles occur frequently as scaffold elements in natural products and bioactive compounds. Herein, we reveal a conceptionally novel photochemically triggered cascade process to these scaffolds. Key to the cascading ring expansion process is an unprecedent intramolecular alkyne-de Mayo reaction.*

The photochemically triggered (2+2) cycloaddition of α,β-unsaturated carbonyl compounds and alkenes is a widespread method for cyclobutane synthesis.[1] Deployment of cyclic vinylogous carboxylic acid derivatives in photochemically triggered (2+2) cycloadditions affords π-acceptor-π-donor-substituted cyclobutanes.[2] Such annulated cyclobutanoids can be susceptible to ring opening to provide medium-sized rings. In the event the ring-opening of a (2+2) photoadduct proceeds via a retro-aldol type bond reorganization, the ring-enlargement process may be classified as (alkene-)de Mayo reaction.[3] Analogously, vinylogous amides and imides can be amenable to (2+2) photocycloaddition/retro-Mannich reaction cascades (aza-de Mayo reaction).[4]

Alkynes are frequently utilized in (2+2) photocycloadditions.[5] However, the de Mayo reaction deploying alkynes (alkyne-de Mayo reaction) has only sparsely been studied. The few published attempts afforded low yields and/or triggered decomposition (Figure 1). Cavazza and Pietra revealed a single low-yielding intermolecular example for the alkyne-de Mayo reaction of **1** to afford **2**;[6] Tedaldi and Baker later reported that the irradiation of **3a** only triggered degradation.[7] Despite these few and discouraging literature precedents, we were intrigued by the prospect of developing the intramolecular alkyne-de Mayo reaction to a versatile synthetic tool for the construction of annulated medium-sized carbacycles (**5**) starting from readily available vinylogous carboxylic acid derivatives (**3**) (Figure 1).

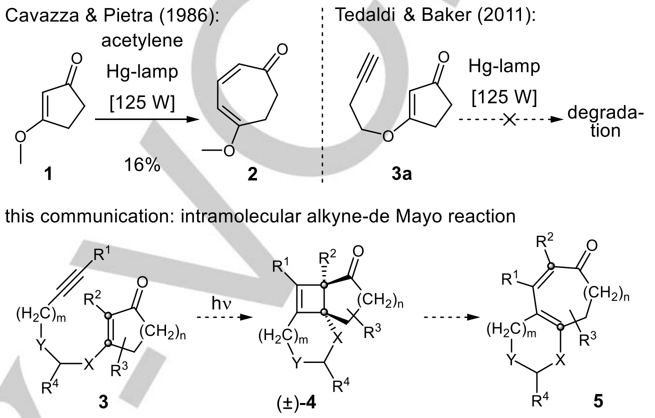

Figure 1. Literature precedents and research outline.

The reports by Cavazza as well as Tedaldi served as starting point for method development (Figure 1). We surmised that the usage of broad-band emitting medium-pressure mercury vapor lamps were responsible for degradative secondary photochemical processes.[8] Therefore, we started to investigate the alkyne-de Mayo reaction of the vinylogous ester **3b** deploying narrow-band emitting light sources (Table 1). The UV/vis spectrum[9] of **3b** in acetonitrile indicates a strong absorption maximum at 231 nm (ε = 23063 $M^{-1}cm^{-1}$; assignable to the allowed π,π* transition) and a weak, broad absorption maximum at 274 nm (ε = 499 $M^{-1}cm^{-1}$; assignable to the forbidden n,π* transition). When irradiating a solution of **3b** in acetonitrile for 12 h using fluorescent lamps emitting at 300 nm, the desired cycloheptadienone **5b** was isolated in 49% yield along with unconsumed **3b** (Table 1, Entry 1). Subjecting **3b** to the identical conditions for 24 h resulted in the isolation of **5b** in 61% yield and recovered **3b** (Entry 2). Further prolonged irradiation increased the yield of **5b** to 65**%** but did not trigger complete consumption of **3b**, and promoted the formation of unidentifiable degradation products (Entry 3). Notably in this regard, the UV/vis spectrum[9] of **5b** in acetonitrile displays a strong and broad absorption maximum at 351 nm (ε = 3466 $M^{-1}cm^{-1}$; assignable to the π,π* transition). Consequently, the prolonged irradiation of the substrate(**3b**)/product(**5b**) mixture in acetonitrile at 300 nm may have triggered the formation of degradation products.[10] In order to avoid product degradation and to support selective π,π* substrate excitation, we turned to *quasi*-monochromatic low-pressure mercury vapor lamps emitting at 254 nm. In the event, irradiation of **3b** in acetonitrile for only 6 h afforded **5b** in 66% yield (Entry 4). Running the reaction at 254 nm in Et_2O or CH_2Cl_2 led to markedly decreased yields (Entry 5–6). Switching to solvent systems capable of hydrogen-bonding resulted in rate-acceleration and improved yields (Entry 7–10). Perfluorinated alcohols turned out to be particularly supportive enabling yields >90% after 3 h of

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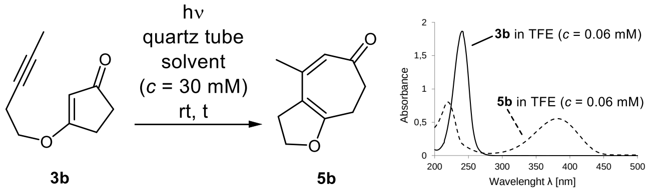
irradiation at 254 nm (Entry 11–12); compromising between cost and selectivity, we selected CF_3CH_2OH (TFE) over $(F_3C)_2CHOH$ (HFIP) for further investigations. Surprisingly, irradiation of **3b** using fluorescent lamps (300 nm) in TFE for 12 h led to the isolation of **5b** in 51% yield along with unconsumed **3b** (33%) indicating no effect of the solvent on the rate of the intramolecular alkyne-de Mayo reaction at 300 nm (Entry 13). Finally, a control experiment demonstrated that solvents should be degassed to avoid decomposition (Entry 14).

Table 1. Alkyne-de Mayo reaction: Optimization[a]



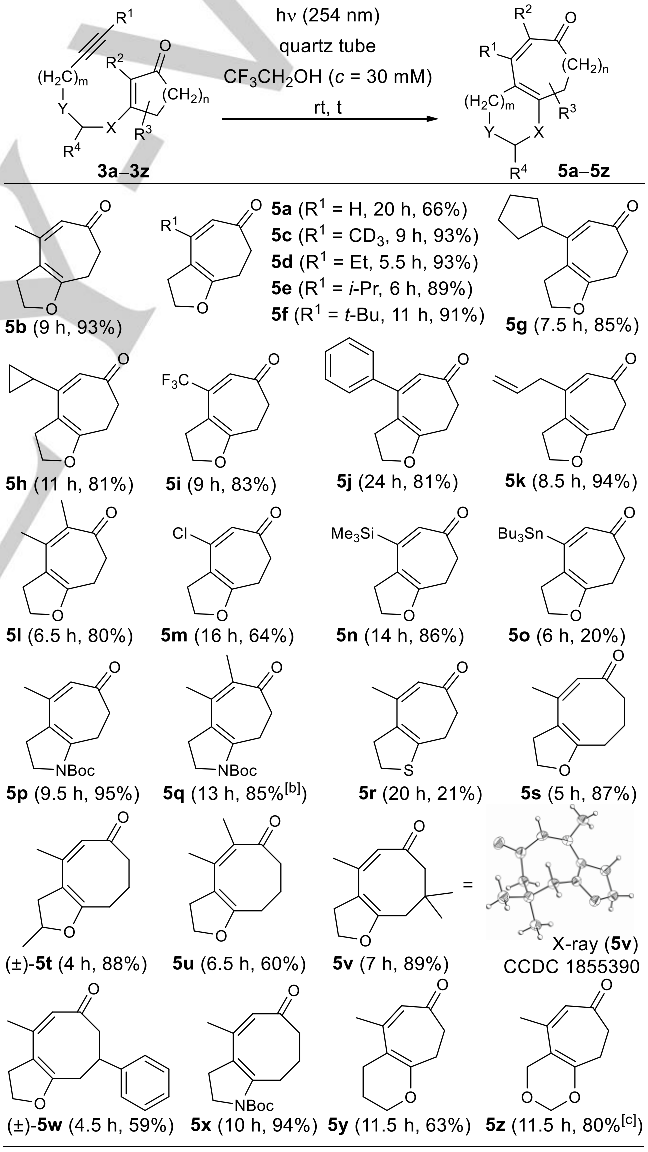
3b **5b**

Entry	λ [nm] [b]	Solvent	t [h]	Yield [%] [c]
1	300	CH_3CN	12	49
2	300	CH_3CN	24	61
3	300	CH_3CN	48	65
4	254	CH_3CN	6	66
5	254	CH_2Cl_2	6	30
6	254	Et_2O	6	14
7	254	$CH_3CN–H_2O$ (1000:1)	6	68
8	254	$CH_3CN–H_2O$ (10:1)	4	83
9	254	$CH_3CN–H_2O$ (1:1)	4	84
10	254	CH_3OH	4	88
11	254	CF_3CH_2OH	3	93
12	254	$(F_3C)_2CHOH$	3	95
13	300	CF_3CH_2OH	12	51
14	254	CF_3CH_2OH [d]	3	decomp.

[a] Performed in degassed solvent (5.2 mL) with 0.16 mmol of **3b** using low-pressure mercury vapor lamps. [b] See the Supporting Information for the emission spectra of low-pressure mercury lamps. [c] Isolated yield after purification by chromatography. [d] Saturated with oxygen.

Having established conditions for the alkyne-de Mayo reaction, we studied scope and limitations by variation of scale, substituents ($R^{1–4}$), linker atoms (X; Y), and ring-size (m = 0–1; n = 1–2) (Table 2). Performing the photoreaction of **3b** on a 1.5 mmol scale required an increased time of irradiation (9 h) but did not affect the yield (93%). Irradiation of **3a** with R^1 = H, initially used without success by Tedaldi and Baker (Figure 1), triggered formation of **5a** in 66% yield. This result emphasizes the pivotal importance of the setup of the photochemical experiment. Further efforts aimed to unveil limiting substituent effects by variation of R^1. However, saturated and unsaturated aliphatic, including the cyclopropyl ("radical clock") substituent, and aromatic substituents were well tolerated, and the corresponding cycloheptadienones **5c**–**5l** could be isolated in yields ranging from 80% to 94%. Further expanding the scope by incorporation of heteroatom substituents afforded the ring-expansion products **5m** (R^1 = Cl, 64%) and **5n** (R^1 = $SiMe_3$, 86%). Finally, for R^1 = $SnBu_3$ we noticed a diminished chemoselectivity and **5o** was isolated in only 20% yield.[11] Aiming to establish an alkyne-aza-de Mayo reaction, vinylogous imide **3p** with X = NBoc and R^2 = H was subjected to the optimized conditions. In the event, we isolated a product mixture consisting of the expected ring expansion product **5p** as well as the proposed yet elusive cyclobutene intermediate **4p**.[12] Notably, stirring a solution of purified **4p** in TFE (c = 30 mM) at 80 °C for 20 min without irradiation led to complete conversion of **4p** to **5p**. Apparently, cyclobutene ring-opening is thermally induced and not photochemically triggered.[13] Complete conversion of the vinylogous imide **3p** to **5p** under the conditions of the photochemical experiment was achieved after 9.5 h and **5p** was isolated in 95% yield. Interestingly, rate-retardation of the ring-opening was also notable for X = NBoc and $R^1 = R^2 = CH_3$ as irradiation of **3q** for 13 h afforded a mixture consisting of **4q** and **5q**. Complete conversion to **5q** was achieved by heating in TFE (c = 30 mM, 80 °C, 70 min). Ring-expansion of the vinylogous thioester **3r** required 20 h of irradiation and afforded **5r** in 21% yield along with the photocycloadduct **4r** (6%)[14] and byproducts useful for mechanistic analysis (*vide infra*).

Table 2. Alkyne-de Mayo reaction: Scope [a]



3a–**3z** **5a**–**5z**

5b (9 h, 93%)

5a (R^1 = H, 20 h, 66%)
5c (R^1 = CD_3, 9 h, 93%)
5d (R^1 = Et, 5.5 h, 93%)
5e (R^1 = *i*-Pr, 6 h, 89%)
5f (R^1 = *t*-Bu, 11 h, 91%)

5g (7.5 h, 85%)

5h (11 h, 81%) **5i** (9 h, 83%) **5j** (24 h, 81%) **5k** (8.5 h, 94%)

5l (6.5 h, 80%) **5m** (16 h, 64%) **5n** (14 h, 86%) **5o** (6 h, 20%)

5p (9.5 h, 95%) **5q** (13 h, 85%[b]) **5r** (20 h, 21%) **5s** (5 h, 87%)

(±)-**5t** (4 h, 88%) **5u** (6.5 h, 60%) **5v** (7 h, 89%)

(±)-**5w** (4.5 h, 59%) **5x** (10 h, 94%) **5y** (11.5 h, 63%) **5z** (11.5 h, 80%[c])

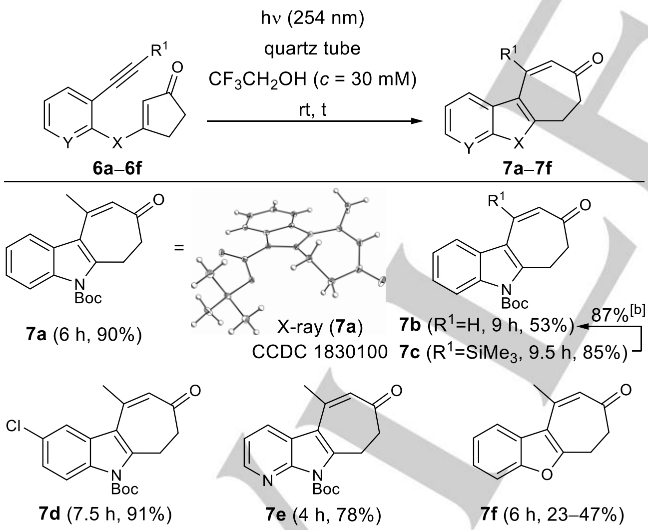
[a] Reactions were performed in degassed CF_3CH_2OH (50 mL) with 1.5 mmol of **3a**–**3z** at 254 nm using low-pressure mercury vapor lamps. Isolated yields after purification by chromatography. [b] Contaminated with the putative cyclobutene **4q** (approx. 15% w/w). [c] After being irradiated for 11.5 h, the

reaction mixture was placed into a pre-heated oil bath (80 °C) and stirred at 80 °C for 2 h.

In order to study ring-size effects for n = 2, **3s**–**3x** were subjected to our optimized conditions and **5s**–**5x** were isolated in yields ranging from 59% to 94%.[15] Finally, alternative tethers were investigated. Irradiation of **3y** with *m* = 1 and Y = CH_2 delivered the dihydropyrane **5y** in 63% yield. Intriguingly, irradiation of the methylene acetal **3z** with m = 1 and Y = O triggered formation of a mixture consisting of the cyclobutene **4z** and the ring expanded product **5z**. Complete conversion to the desired cycloheptadienone **5z** then required heating the mixture in TFE (80 °C, 2 h). This second-generation linker (X = Y = O) should be amenable to straightforward linker cleavage using Brønsted or Lewis acidic conditions.[16]

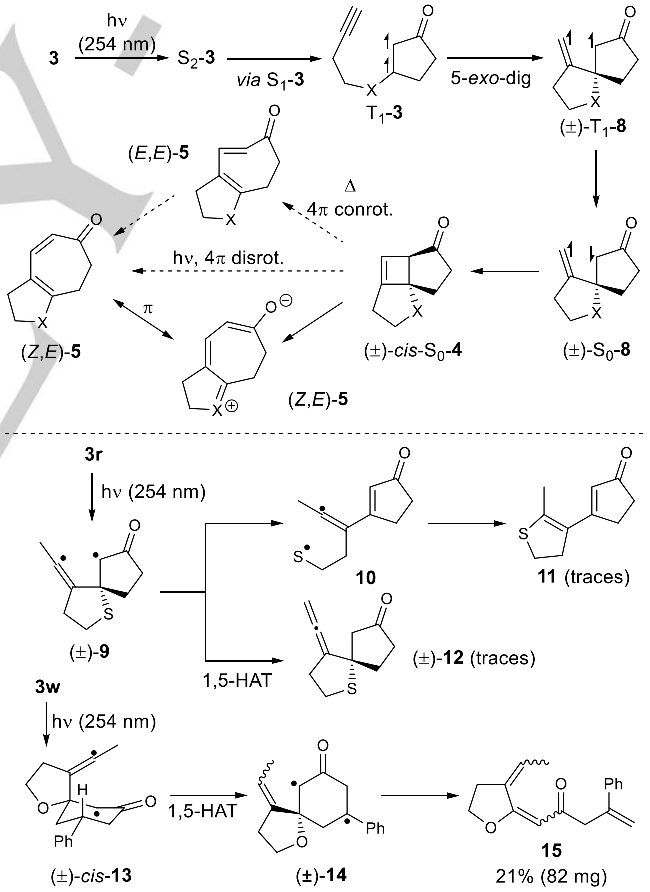
Cyclohepta[*b*]indole and cyclohepta[*b*]benzofuran structural motifs are eminent as scaffold elements in natural product and medicinal chemistry.[17],[18] Aiming to establish a metal-free single-step annulative access to these scaffolds, we studied the photochemistry of **6a**–**6f** (Table 3). To our delight, subjecting the vinylogous imides **6a** and **6c**–**6e** to the previously optimized conditions afforded the cyclohepta[*b*]indolones **7a** and **7c**–**7e** in yields ranging from 78% to 91%.[15] In contrast, irradiation of **6b** resulted in the formation of **7b** in only 53% yield along with some decomposition. However, treating **7c** with TBAF smoothly provided the desired protodesilylated cyclohepta[*b*]indolone **7b** in 87% yield. Subjecting the corresponding vinylogous ester **6f** to the identical conditions afforded the cyclohepta[*b*]benzofuranone **7f** in inconsistent yield (23–47%) along with yet unidentified byproducts.

Table 3. Alkyne-de Mayo reaction: Cyclohepta[*b*]indoles [a]



[a] Reactions were performed in CF_3CH_2OH (5.2 mL) with 0.16 mmol of **6a**–**6f** at 254 nm using low-pressure mercury vapor lamps emitting. Isolated yields after purification by chromatography. [b] TBAF (1.2 equiv), THF, 0 °C, 15 min.

Mechanistically, we propose that irradiation at 254 nm causes population of the excited state $S_2(\pi,\pi^*)$ followed by an internal conversion to $S_1(n,\pi^*)$ (Scheme 1). Rapid intersystem crossing to T_1-**3** triggers 5-*exo*-dig cyclization to the 1,4-biradical T_1-**8**. Subsequent transition to S_0-**8** is followed by cyclobutene ring-closure to afford *cis*-S_0-**4**.[19] Our proposal of the intermediacy of spiro-1,4-biradicals is supported by the isolation of unexpected byproducts from interfering hydrogen atom transfer reactions (Scheme 1). The ring-opening of the intermediate tricyclic cyclobutene S_0-**4** may be considered as a stereospecific conrotatory electrocyclic ring-opening. However, the conrotatory pericyclic bond reorganization would deliver the strained ring expansion product (*E*,*E*)-**5**. A rapid double bond isomerization of (*E*,*E*)-**5** to (*Z*,*E*)-**5** under irradiation and in the presence of a nucleophilic solvent appears possible. Alternatively, the ring-opening may procced by a retro-aldol (X = O) or retro-Mannich-type (X = NBoc) mechanism to provide (*Z*,*E*)-**5** directly and without the intermediate formation of strained (*E*,*E*)-**5**.[20] The assumption of a polar concerted but non-pericyclic ring opening would nicely explain the beneficial effect of hydrogen-bonding polar protic solvents on the rate and the yield of the ring-opening reaction. The rate difference of the ring opening for X = O and X = NBoc may be rationalized from the same point of view: the restricted availability of the lone pair of the nitrogen atom of the NBoc functionality may retard the retro-Mannich type ring opening reaction thus leading to a slow conversion and the experimental observation of tricyclic cyclobutene intermediates.



Scheme 1. Mechanistic hypothesis and supportive experimental results.

In summary, the intramolecular de Mayo reaction is not restricted to alkenes. Employment of alkynes empowers a one-pot metal-free entry to annulated medium-sized rings and cyclohepta[*b*]indoles. Key to success in developing an alkyne-de Mayo reaction was the deployment of a *quasi*-monochromatic light source and a polar protic solvent. Valuable applications of the alkyne-de Mayo reaction in target-oriented synthesis are easily conceivable.[21]

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Keywords: cascade reaction • cycloaddition • cyclohepta[*b*]indole • photochemistry • ring expansion

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[13] For computational studies on the thermodynamics of the ring-expansion of **3b**, see the Supporting Information.

[14] Contaminated with the allene **12**.

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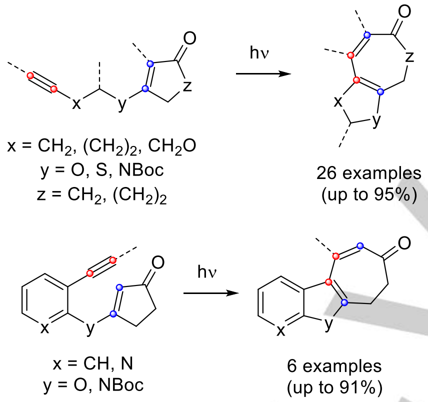
Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

Enlightened and expanded: The de Mayo reaction is not restricted to alkenes. Deployment of a *quasi*-monochromatic light source and a hydrogen bonding polar protic solvent enabled the development of an alkyne-de Mayo reaction. This broadly applicable method provides rapid access to medium-sized carbacycles and cyclohepta[*b*]indoles starting from straightforwardly accessibly vinylogous carboxylic acid derivatives.



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